Study of efficacy and safety oral ivermectin in the prophylaxis of COVID-19 disease in post-exposed to COVID-19 individuals by close contact or epidemiological nexus

INTRODUCTION

1. Characteristics of SARS-CoV-2 and clinical course

In December 2019, from the detection of pneumonia of unknown origin in the city of Wuhan (China), a new type of coronavirus (SARS-CoV-2) was identified[1], whose spread generated one of the greatest global public health crises of this generation, accompanied by severe socio-economic consequences worldwide[2,3]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a single-stranded RNA virus that causes severe acute respiratory syndrome.

The association between SARS-CoV and SARS-CoV-2 was early supported by the analyzes made to the protein S (spike) that characterizes both viruses, so it was clear that there was an important similarity between these transmembrane structures, making them practically super imposable each. The only portion that is significantly different is a furin-binding domain in the SARS-CoV-2 protein S, which has been speculated that it could expand the tropism or increase the transmissibility of the virus, compared to the SARS-CoV of 2003. [4]

On the other hand, one of the most conserved portions of the protein is the receptor-binding domain (RBD), which has a similar affinity (and that according to reports may be higher) to the angiotesin converting enzyme type 2 (ACE2) in compared to SARS-CoV[4] . This functional receptor is found in tissues such as the alveolar epithelium of the lung, arterial and venous endothelium, smooth muscle, renal tubular epithelium, and small intestine epithelium, which largely explains the symptoms and clinical presentation of patients with COVID-19[5].

Regarding the clinical presentation of the patients, it has been calculated that the incubation period of the virus is 5.1 days (95% CI 4.5 to 5.8 days), and that 97.5% of the patients will present symptoms at 11 days (95% CI 8.2 to 15.6 days). The average patient with COVID-19 presents the following symptoms: fever (78%), cough (60-79%), and myalgia or fatigue (35.8 to 44%); 55% develop dyspnea, which appears on average 8 days after the onset of symptoms. Mortality has been calculated to be 5.7%, according to the study "Real Estimates of mortality following COVID-19" by Baud et al.[6] To the presentation of the symptoms, we must add the comorbidities that accompany

each patient and that can negatively affect their diagnosis[4]. It is currently considered that, in at least one group of patients, severe symptoms are related to a cytokine storm produced in the context of acute respiratory distress syndrome that leads to impaired lung function.[7]

The severity of COVID-19 disease is associated with a cytokine profile, which resembles that of secondary hemophagocytic lymphohistiocytosis (sHLH), and is characterized by an increase in interleukin (IL) -2, IL-7, factor granulocyte colony stimulant, interferon-γ inducible protein 10, monocyte chemo attractant protein 1, macrophage inflammatory protein 1 -α, and tumor necrosis factor-α. Mortality predictors from a recent retrospective, multicenter study of 150 confirmed COVID-19 cases in Wuhan, China, included elevated ferritin (mean 1297.6 ng / ml in non-survivors vs 614.0 ng / ml in survivors; $p < 0.001$) and IL-6 ($p < 0.0001$,) suggesting that mortality could be due to viral hyperinflammation[7]. However, cases have been reported where tissue and organ involvement was found whose concentration of ECA2 receptors is very dissimilar (myocardium, brain). In all of them, the common denominator was small vessel thrombosis, as observed in entities such as Catastrophic Antiphospholipid Syndrome (SAC) and Disseminated Intravascular Coagulation (DIC).[7]

On the other hand, a large number of patients with COVID-19 presented mild or no symptoms, a factor that increased, due to the high level of contagion of this virus, the possibility of its rapid spread in the community[4].

2. Drug repositioning

The abrupt onset and rapid dissemination of SARS-CoV-2, limited the times for the design and evaluation of specific drugs, therefore, together with the measures of rapid diagnosis and isolation, and the development of vaccines that immunize the population against the virus, “pharmacological repositioning” measures have been chosen, in an effort to find effective therapies that counteract the most serious effects of the disease, which constitute approximately 15% of cases, according to the World Organization Of the health[6–8].

The repositioning of existing drugs on the market, with established safety profiles, which are applied to other therapeutic indications, is a pragmatic strategy (which has already had good results with other drugs), cheaper and

faster than the development of new drugs, and it can be a key tool in an emergency situation such as the current one. [9,10]

Considering that to date there are no specific therapies approved by the United States Food and Drug Administration (FDA) for SARS-CoV-2, different repositionable drugs are being investigated in clinical trials and compassionate use protocols based on in vitro activity (against SARS-CoV-2 and other related viruses) and / or in the limited clinical experience available. These studies are currently in different phases, and some have already shown encouraging results in terms of their efficacy in treating the disease.

3. Mechanisms of action of ivermectin and background

In relation to ivermectin, there are several studies in progress and others completed, both for prophylactic use, as well as for treatment in mild and severe cases of COVID-19. Studies by Caly et al., Based on previous experience with ivermectin and its action on other viruses, suggest that ivermectin has an inhibitory effect on SARS-CoV-2. [11–13]

Ivermectin was first introduced commercially in 1981 for use in animals, and was subsequently used for various diseases in humans. It has shown a wide range of activities, ranging from endo/ectoparasitide activity, to antiviral, antibacterial and anticancer activity[14]. Since 1980 it has been included in the essential drugs list of the World Health Organization (WHO), with millions of doses delivered annually through mass drug distribution programs[13].

The first report on the efficacy of ivermectin *in vivo,* was that of its effect on parvovirus's in a freshwater crab (Cherax quadricarinatus) fifteen. The studies by Caly et al. Along with those of other groups, they have also demonstrated the efficacy of their antiviral activity against a wide range of viruses *in vitro.* It has been confirmed to inhibit IN nuclear import and replication of HIV-1[15]. Ivermectin has also been shown to inhibit nuclear import of viral and host proteins, including non-structural protein 5 from simian virus SV40 (T-ag) and dengue virus (DENV)[12].

It has been shown to limit infection by RNA viruses such as DENV 1-4, West Nile virus, Venezuelan equine encephalitis virus (VEEV), and influenza, and this broad-spectrum activity is believed to be due to to the action of many different

RNA viruses on IMPα / β1 during infection[12]. Ivermectin has also been shown to be effective against DNA pseudorabies virus (PRV), against Zika virus (ZIKV) in mice, but the authors acknowledged that study limitations warranted reassessment of ivermectin's activity against ZIKV[11,12,16].

The causative agent of the current COVID-19 pandemic, SARS-CoV-2, is a single-stranded, positive-sense RNA virus that is closely related to the severe acute respiratory syndrome coronavirus (SARS-CoV)[11].

Studies of SARS-CoV proteins have revealed a possible role of IMPα / β1 during infection in the signal-dependent nucleocytoplastic closure of the SARS-CoV nucleocapsid protein, which may affect cell division[11].

Furthermore, the SARS-CoV accessory protein, the ORF6 protein, has been shown to antagonize the antiviral activity of the transcription factor STAT1 by sequestering IMPα / β1 in the ER / Golgi rough membrane. Taken together, these reports suggest that the nuclear transport inhibitory activity of ivermectin may be effective against SARS-CoV-2[11].

On the COVID-19 virus, ivermectin would have two types of action: extra and intracellular[3]. The extracellular action is through interaction with cavities or ionophore channels present in the sarcolemma of the cell membrane, which electrolytically trap the corona of the virus capsid and prevent access to the cell[3]. In the mechanism intracellular, it is carried out through a destabilization of the IMPORTINE heterodimer complex (IMPA alpha / b1), a cotransporter that would carry the virus to the nucleus. When destabilized, the entry of the virus to the nucleus is blocked and thus prevents viral replication[3].

To this day, numerous clinical trials are being conducted around the world to evaluate the antiviral activity of ivermectin in the treatment (in mild and severe cases) and prophylaxis against COVID-19. In the database of the US National Library, you can find about 60 clinical studies in different phases, some of which have already yielded results. These essays can be accessed through https://www.clinicaltrials.gov/

In Tucumán, the IVERCAR-TUC protocol (NCT Clinical Trials NCT04701710) evaluated the effect of the use of ivermectin associated with iota-carrageenan in repeated doses in the oral cavity for prophylaxis in the group of health personnel. The use of both associated drugs would reduce the probability of the

appearance of severe clinical manifestations of the disease, and reduce the viral load and the time of dissemination of the virus in the preclinical phase[17]

On the other hand, the IDDEA protocol proposes the hypothesis of the use of ivermectin, dexamethasone, vitamin D3, enoxaparin and aspirin (according to the degree of symptoms), to reduce the risk of hospitalization in mild patients and mortality in severe patients. Both studies have demonstrated efficacy and safety based on the primary and secondary endpoints of ivermectin in relation to COVID-19 [18,19]

4. Pharmacokinetics and Safety of Oral Ivermectin

Ivermectin is authorized by the FDA (Food and Drug Administration), authorities of high sanitary surveillance and ANMAT, in the pharmaceutical forms tablets and oral solution for systemic absorption, and for topical administration as cream at 0.5% and 1%[20]. After its metabolization in the human body, its metabolites are almost exclusively eliminated in the faeces for about 12 days, while less than 1% of the administered dose is excreted in the urine. The plasma half-life of ivermectin is around 12 hours and that of the metabolites around three days.

Studies have shown the effectiveness of oral ivermectin in the treatment of endoparasites and ectoparasites. There are reports of its management in scabies, myiasis, onchocerciasis, migraine larvae of the skin and even pediculosis, to the point that today it is the drug of choice for the treatment and control of onchocerciasis[13]. The side effects that have been reported are fever, headache, pruritus, edema, myalgia and arthralgia in 64% of them with the first dose, and 50% with the second, but of mild to moderate intensity, which subsided easily with aspirin and / or antihistamines.

Other observed effects were dizziness, drowsiness, and hypotension, which are mild and brief [13,20]. The drug is well tolerated in children older than 5 years, and administered orally, it does not cross the blood-brain barrier. It is contraindicated in pregnancy, although studies have been reported in which it was inadvertently administered to women in the first trimester of pregnancy without finding teratogenic effects. Its concomitant use with drugs that act on GABA receptors, barbiturates and benzodiazepines should be avoided [13]

5. Repositioning of ivermectin for the treatment and prophylaxis of COVID-19

Taking into account the above, and the imperative of reducing hospital admissions and the mortality rate, while optimizing health HR, our health system considered the study of the repositioning of the drug ivermectin for treatment and prophylaxis of COVID as strategic[18].

As previously evaluated in health personnel, associated with iota-carrageenan (IVERCAR-TUC), in this case we seek to evaluate the effect of the use of oral Ivermectin on the appearance and eventual progression of COVID-19 disease in a population of healthy individuals who are exposed to contagion through close contact with a positive case of COVID-19 or epidemiological link.

OBJECTIVES, HYPOTHESIS AND VARIABLES OF THE STUDY

a. Objective

To evaluate the effect of the use of Ivermectin on the appearance and eventual progression of COVID-19 disease in a population of healthy individuals who have been found exposed and with a higher risk of contagion due to being close contact or epidemiological link

b. Study hypothesis

Treatment with ivermectin would decrease the probability of the appearance or progression of clinical manifestations and the appearance of severe disease, and decrease the viral load and the time of virus shedding.

c. Study variables

Comparison between both treatment groups of the following variables:

Primary

- Incidence of appearance of symptoms related to infection by
- CoVid-19 Duration of symptoms secondary to infection by Covid -19
- Incidence of progression to severe disease
- Incidence of clinical fall or relapse after discharge, in cases who contract CoVid-19
- Incidence of reported adverse events

Secondary

- Incidence of CoVid-19 detection

- Virus persistence time

SYNOPSIS OF THE STUDY

Code of Protocol	Addendum Exp: 5077/410-CH-2020 IP Dra. Rossana Chahla - Dr. Luis Medina Ruiz
Medical Executive	Secretary Monitor Center SIPROSA Presidency Avellaneda Hospital
Title of study	Safety and Efficacy Study of oral Ivermectin in the prophylaxis of COVID-19 disease in individuals post-exposure by close contact or epidemiological link.
Type of study	Randomized, blinded, placebo-controlled clinical trial with Control Group (CG) and Treatment Group (GT). Randomization 2:1. Treatment group n = 500. Placebo group n = 250
Justification	The emergency of COVID-19 requires the rapid development of strategies to avoid the impact of the disease on the population, to reduce the saturation of our health system and to reduce the level of mortality from coronavirus. Taking into account the characteristics of the RNA detection diagnostic test, which is not immediate, and that contagion control is essential during the first days of the development of the disease this treatment with ivermectin in suspected cases of COVID-19 (by epidemiological link) would contribute to the control of contagion during the first part of the infection, even in the absence of symptoms of the disease.
Hypothesis of the study	Treatment with ivermectin would decrease the probability of the appearance or progress of clinical manifestations and the appearance of severe disease, and would decrease the viral load and the time of virus shedding.
Objective	To evaluate the effect of the use of Ivermectin on the appearance and eventual progression of COVID-19 disease in a population of healthy individuals who have been exposed and at higher risk of infection due to close contact or epidemiological link
Variables of Study	Comparison between both treatment groups of the following variables: Primary: • Incidence of onset of symptoms related to CoVid-19 infection. • Duration of symptoms secondary to Covid infection -19. • Incidence of progression to severe disease. • Incidence of fall or clinical relapse after discharge, in cases that contract CoVid-19. • Incidence of reported adverse events. Secondary: • CoVid-19 detection incidence. • Virus persistence time
Poblation	It will be constituted by healthy individuals that are exposed and with greater risk of contagion of COVID-19 by

	being close contact or epidemiological nexus. A total of 750 individuals that meet the inclusion criteria will be included
Elegibility criteria	**Inclusion:** 1. Over 18 years of either sex 2. Women of childbearing age with a pregnancy test negative 3. In a group, close contact or epidemiological link 4. Able to understand and give informed consent written. 5. RT-PCR test with negative result. **Exclusion:** 1. Known hypersensitivity or allergy to any component of the product under evaluation. 2. Age under 18 years. 3. Use of immunosuppressants (including corticosteroids systemic) in the last 30 days. 4. Pregnant or nursing. 5. Patients with other acute infectious diseases.8 6. Patients with autoimmune disease and / or diseases unbalanced chronicles. 7. Who have received a vaccine for Covid 19 (1/2 dose) or who have taken ivermetin (prior to 30 days of the study) or who are participating in another COVID prophylaxis study. **Discontinuation:** 1. Development of any serious adverse drug reaction or that, at the discretion of the investigator, puts the subject at risk in study 2. Development of symptoms or positive test for COVID-19
Intervention	Randomization to Treatment Group Ivermectin 0.6mg / kg of weight in two intakes (1st take on day 1 and 2nd take on day 7) vs. Placebo, two takes (1st takes day 1 and 2nd takes day 7). Control at day 7, final period of intervention. It will be indicated for the best absorption of ivermectin that it is administer during lunch. The dose will be controlled by kg of weight, not exceeding in any case (in individuals over 70 kg) the 7 tablets per dose
Intervention	The study lasts 14 days. Intervention period: 7 days Post-intervention follow-up period: 14 days If the patient presents symptoms and a positive test for COVID-19, suspends research treatment to be cared for by the health personnel with standard care for coronavirus infection and a post-intervention follow-up period of 21

	days will be indicated. • Visit 0 = Day 0: Information about the study to the patient and signature of the informed consent. Affiliation data, clinical control, registration of comorbidities, and taking RT-PCR • Visit 1 = Day 1: PCR results. Enrollment in the study. Randomization to treatment or placebo Dispensing the drug or placebo • Day 4: Remote monitoring. Control of symptoms and side effects • Visit 2 = Day 7: Dispensing of the 2nd dose. Control of symptoms and side effects • Visit 3 = Day 14: Control of symptoms and effects collateral. Post follow-up completion RT-PCR test intervention
Statistical Analysis	Descriptive statistics of all variables will be presented analyzed. To compare continuous variables, a test will be used or Wilcox on test, while, for non-continuous variables or categorical, a chi-square or Fisher test will be used. For analysis of interaction of variables, multivariate logistic regression will be used safety analysis will present the incidence rate of AE reported describing its severity and its relationship with the treatment in study.

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